

### Remarks

Claims 1, 3-12, 25-29, 36 and 37 are pending in the application after entry of the herein amendment. Claims 26-29 stand withdrawn pursuant to a restriction requirement. The claims of Group I (claims 1, 3-12, 25 and 37) have been elected for examination. Claims 6 and 36 of the elected group are presently withdrawn from consideration as being directed to non-elected species.

Claims 1 and 26 have been amended to recite that the formulation is in the form of a freeze-dried matrix. Support for the amendment is found, for example, at page 14 of the specification, line 24, and page 17, lines 1-23. Claim 25 has been amended to address the Section 112 rejection. Support for the amendment is found in original claims 23 and 25.

Claims 16-19 and 30-35 have been cancelled. Claims 1, 3-5, 7-12 and 25 are under consideration. Reconsideration of all grounds of rejection is requested in view of the above changes, and the following remarks.

All claims amendments and claim cancellations are made without prejudice to the filing of one or more continuing applications.

### Response to 35 USC 112 Rejection

Claim 25 has been amended to overcome the rejection, providing antecedent basis for the recitation of a waxy starch.

### Response to 35 USC 103 Rejection

Claims 1-5, 7-12, 16, 23, 25 have been rejected under 35 USC § 103 (a) as being unpatentable over Kaper et al (EP 0242913 A2) in view of Burgoyne et al (US 6,046,185). Examiner acknowledges that EP 0242913 A2 is a member of the same patent family as US 4,780,149, both patent documents deriving priority from NL 8600937.

Claims 2, 16 and 23 have been cancelled. Applicants will respond to the rejection as it related to claims 1, 3-5, 7-12 and 25.

Claim 1 has been amended to recite a bioadhesive pharmaceutical formulation in the form of a freeze dried matrix. Thus, claim 1 recites a bioadhesive pharmaceutical formulation

comprising an active agent and a mucoadhesive carrier for the active agent, wherein the mucoadhesive carrier comprises a  $\beta$ -limit dextrin, *wherein the formulation is in the form of a freeze-dried matrix*. The same amendment has been made to withdrawn claims 26 for purposes of rejoinder of that claim. Neither Kaper nor Burgoyne provide for formulations of  $\beta$ -limit dextrans where the formulation is freeze dried or lyophilized in any way.

### *The Invention*

Freeze drying, lyophilization or cryodesiccation, is a dehydration process typically used to preserve a perishable material or make the material more convenient for transport. Freeze drying works by freezing the material and then reducing the surrounding pressure and adding enough heat to allow the frozen water in the material to sublime directly from the solid phase to the gas phase. There are three stages in the complete freeze drying process: freezing, primary drying and secondary drying. Freeze drying and lyophilization are terms that are well known, and the techniques are well understood.

Freeze drying the formulation of the present invention has the surprising effect that it creates a porous freeze dried matrix which is able to carry active agents dispersed therein. The ability to hold active agents in this porous freeze dried matrix has been found by the inventors to be unique to formulations comprising  $\beta$ -limit dextrin (specification, page 17, lines 8-11). The  $\beta$ -limit dextrin is uniquely able to retain this freeze dried porous structure and is uniquely able to hold active agents for administration. The  $\beta$ -limit dextrin is hydrolyzed by the  $\alpha$ -amylase in the mouth which allows the active to be released in the mouth thereby enabling administration of drugs mucosally thus avoiding the stomach and the gastrointestinal tract. The freeze dried porous matrix also has the advantage of making the formulation bioadhesive, and specifically mucoadhesive. As the formulation is bioadhesive/mucoadhesive, it sticks to the oral mucosa where it disintegrates quickly when hydrated by the saliva (specification, page 17, lines 14-21). The quick disintegration is facilitated by the rapid hydrolysis of the  $\beta$ -limit dextrin by the  $\alpha$ -amylase present in the mouth, resulting in the rapid release of active agents in the oral cavity.

The applicants note that the only comparable products on the market to date which "melts in the mouth" are gelatin based breath fresheners and the like. These have the disadvantages that

they are not suitable for use by vegans and vegetarians or by certain religious groups and in that they have the potential to carry and spread for example prion based diseases. In addition, gelatins are not hydrolyzed by salivary enzymes (they are hydrolyzed by protease-type enzymes, which are absent from the saliva). This is not the case for the  $\beta$ -limit dextrin of the present invention where buccal hydrolysis occurs with salivary  $\alpha$ -amylase, providing a rapid disintegration, oral delivery and associated pleasant (for example, non-gummy) mouth feel. The inventors of the present application have prepared a new formulation comprising  $\beta$ -limit dextrin and in the form of a freeze dried matrix, which is bioadhesive (specifically, the  $\beta$ -limit dextrin is mucoadhesive) and thus uniquely allows the administration of active agents to the oral cavity.

*Kaper et al.*

Kaper discusses the use of  $\beta$ -limit dextrans in pharmaceutical, food and drink applications, but without proposing a specific role for the  $\beta$ -limit dextrin in these materials.

Kaper does not teach a bioadhesive formulation comprising a mucoadhesive carrier which comprises  $\beta$ -limit dextrans wherein the formulation is in the form of freeze dried matrix. Furthermore, there is nothing in Kaper to suggest that such freeze dried matrices would have bioadhesive or mucoadhesive properties, or that they would form a porous structure which enables the encapsulation and rapid oral delivery of active agents. It is critical to freeze dry a formulation of  $\beta$ -limit dextrans in order to achieve the bioadhesive and mucoadhesive properties.

Kaper describes "deep freeze" products, in reference to products that have a "gum structure" (col. 3. lines 29-34). Deep freeze products are products that are intended to be stored in a deep freeze such as, for example, ice cream. In contrast, the present invention relates to a bioadhesive formulation comprising a mucoadhesive carrier which comprises  $\beta$ -limit dextrans wherein the formulation is in the form of freeze dried matrix. As described above, freeze drying is a well known chemical process that involves freezing a material, reducing the surrounding pressure and adding enough heat to allow the frozen water in the material to sublime directly from the solid phase to the gas phase. There are three stages in the complete freeze drying process: freezing, primary drying and secondary drying. Freeze dried products are quite distinct and separate from "deep freeze" products.

Carbohydrates, including dextrans, exhibit different properties in different environments, and depending on the method used to prepare them. The suitability of a carbohydrate for one particular application does not imply or suggest that it will be suitable for another application. For example, the use of malto-dextrans in drinks (to increase viscosity, to stabilize and to provide calories) does not suggest that they are suitable for the formation of films - where in fact they are not suitable.

Kaper cites tablets as examples of pharmaceutical applications in which  $\beta$ -limit dextrans could be used. Using Kaper, one would not expect to make buccal melt systems because tablets are made by compression (not freeze drying), are not porous, are not rapidly hydrated, are not designed to melt in the mouth, and are not designed to be bioadhesive. Even the most rapid tablet delivery formulations cannot match the freeze dried matrices of the present invention for the rate of oral delivery. It would be exceptionally difficult to facilitate rapid release from tablets in the oral cavity as they do not adhere to mucosa or rapidly disintegrate to release active agents.

The knowledge obtained from Kaper that  $\beta$ -limit dextrans can be administered orally does not imply or teach that formulations of  $\beta$ -limit dextrans may take the form of freeze-dried matrices, and does not suggest that those matrices will be bioadhesive and/or mucoadhesive, or suitable for the administration of active agents to the mucosa. There is no evidence in Kaper that freeze dried matrices can be made from  $\beta$ -limit dextrin, that freeze dried matrices have useful delivery applications, that freeze dried matrices could be used for oral delivery, and that matrices made from  $\beta$ -limit dextrin would be bioadhesive and adhere to the mucosa thereby delivering active agents thereto.

There is no motivation in Kaper to develop a bioadhesive or mucoadhesive product which can deliver active agents to the oral cavity. Furthermore, there is no motivation in Kaper to select  $\beta$ -limit dextrans for this purpose. Further still, there is no motivation in Kaper to freeze dry formulations comprising  $\beta$ -limit dextrans for this purpose, nor would there be any expectation that freeze dried formulations comprising  $\beta$ -limit dextrans would successfully produce a product that is bioadhesive or mucoadhesive, and that is able to carry and deliver active agents to the oral cavity, by quickly disintegrating on contact with the mucosa. Therefore the invention of the present application would not be obvious to one of ordinary skill in the art in

view of Kaper.

*Burgoyne et al.*

Burgoyne does not remedy the deficiencies of Kaper. Kaper teaches a pharmaceutical mixture including a pharmaceutically acceptable carrier, which can be a dextrin excipient. However, there is no discussion regarding what type of dextrans can be used as excipients. Moreover, there is no discussion as to the type of excipient that dextrans may provide. For example, excipients can be anti-adherents, binders, coating, disintegrants, fillers, diluents, flavors, colors, glidants, lubricants, preservatives, sorbents or sweeteners. The functionality of dextrans, even linear dextrans, differs dramatically from one dextrin to another, and the utility of a very soluble trisaccharide is completely different to that of a huge molecule such as  $\beta$ -limit dextrin (in terms of functionality). Therefore, one could not extrapolate the properties of a maltodextrin or a cyclodextrin to those of a  $\beta$ -limit dextrin, for example. Even the sub-group of maltodextrans ranges from two to twenty glucose units, all of which are "dextrans", and all of which have different properties. One could not anticipate from the term "dextrin" which particular molecule would be suitable for use in a given application as the properties of the various dextrans are very different. Furthermore, one could not anticipate from the term "dextrin", in which physical form any such dextrin should be used.

There is no teaching or suggestion in Burgoyne that  $\beta$ -limit dextrans can be used in a bioadhesive or mucoadhesive product which can deliver active agents to the oral cavity. In particular, there is no indication that a formulation comprising  $\beta$ -limit dextrans in the form of a freeze dried matrix, would have bioadhesive and mucoadhesive properties. These matrices can be used for the delivery of active agents to the buccal cavity where reaction with water and  $\alpha$ -amylase facilitate the release of the active agents. The freeze dried formulation provides bioadhesive and mucoadhesive properties, which enables the formulation to "stick" to the inside of the mouth where the drug can be absorbed through the mucosa.

The knowledge obtained from Burgoyne that pharmaceutical mixtures can include dextrin excipients does not imply or teach that  $\beta$ -limit dextrans in formulations that are in the form of freeze dried matrices will be bioadhesive and/or mucoadhesive. Nor does this teach that

such formulations will be suitable for the administration of active agents to the mucosa.

There is no motivation in Burgoyne to develop a bioadhesive or mucoadhesive product which can deliver active agents to the oral cavity. Furthermore, there is no motivation in Burgoyne to select  $\beta$ -limit dextrans for this purpose. Further still, there is no motivation in Burgoyne to freeze dry formulations comprising  $\beta$ -limit dextrans for this purpose, nor would there be any expectation that freeze dried formulations comprising  $\beta$ -limit dextrans would successfully produce a product that is bioadhesive or mucoadhesive, and that is able to carry and deliver active agents to the oral cavity, by quickly disintegrating on contact with the mucosa. Burgoyne therefore does not remedy the deficiencies of Burgoyne.

Most significantly, neither Burgoyne nor Kaper teach a formulation of an active agent and a  $\beta$ -limit dextrin as a carrier, wherein the formulation is in the form of a freeze dried formulation. Furthermore, there would have been no motivation in Burgoyne or Kaper to use  $\beta$ -limit dextrans in the form of a freeze dried formulation. Thus, there is no combination of Kaper or Burgoyne that would lead the skilled man to the present invention. There would be no motivation to combine the teachings of Kaper and Burgoyne. Even if one were to combine the teachings of Kaper and Burgoyne, they would not arrive at the present invention. Therefore the invention of the present application would not be obvious to one of ordinary skill in the art in view of Burgoyne in combination with Kaper.

Claims 1, 3-5, 7-12 and 25 are allowable over Kaper in view of Burgoyne.

#### Request for Rejoinder of Claims

Claim 26, currently withdrawn, is directed to a method of delivering an active agent, by administering a formulation having the elements of the formulation of claim 1. In view of the allowability of claim 1, withdrawn claim 26, as well as its dependent claims 27-29 and 37, are now rejoinable pursuant to MPEP 801.04. Rejoinder is requested.


#### Conclusion

The claims remaining in the application are in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted,

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